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Cheyne-Stokes Respiration in Patients with Heart Failure: Prevalence, Causes, Consequences and Treatments

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Key Words

Cheyne-Stokes respiration • Central sleep apnea • Heart failure • Adaptive servo-ventilation

Abstract

Cheyne-Stokes respiration (CSR) is characterized by a pattern of cyclic oscillations of tidal volume and respiratory rate with periods of hyperpnea alternating with hypopnea or apnea in patients with heart failure. CSR harms the failing heart through intermittent hypoxia brought about by apnea and hypopnea and recurrent sympathetic surges. CSR impairs the quality of life and increases cardiac mortality in patients with heart failure. Thus, CSR should actively be pursued in patients with severe heart failure. When CSR persists despite optimal therapy of heart failure, noninvasive adaptive servoventilation is currently the most promising treatment.

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Introduction

Sleep-disordered breathing is common in patients with congestive heart failure (CHF) and is increasingly recognized as an independent risk factor for morbidity

and mortality in these patients [1]. This review focuses on Cheyne-Stokes respiration (CSR), a pattern of waxing and waning of ventilation with periods of hyperpnea alternating with central apnea/hypopnea in heart failure patients. CSR is also observed in certain patients with cerebrovascular strokes [2] and in patients with pulmonary hypertension [3]. CSR, the particular type of periodic breathing associated with heart failure, is characterized by a long hyperpnea phase and a long cycle (fig. 1), which are linked to the prolonged lung to chemoreceptor circulation time in low cardiac output states [4]. CSR is often observed during sleep and is also termed ‘central sleep apnea’ (CSA), but CSR may as well emerge during wakefulness and even during physical activity [5] (fig. 1) [6, 7]. Therefore, CSR in the context of chronic heart failure may be considered a syndrome distinct from other clinical conditions that are also associated with periodic CSA, such as the idiopathic CSA syndrome or high-altitude periodic breathing [8].

Since its first description, 200 years ago, in a patient who suffered from heart failure with atrial fibrillation and had sustained a stroke, CSR has been considered an ominous sign of the gravity of the underlying disease and as a forecast of looming death. In the meantime, scientific evidence has accumulated that proves that CSR

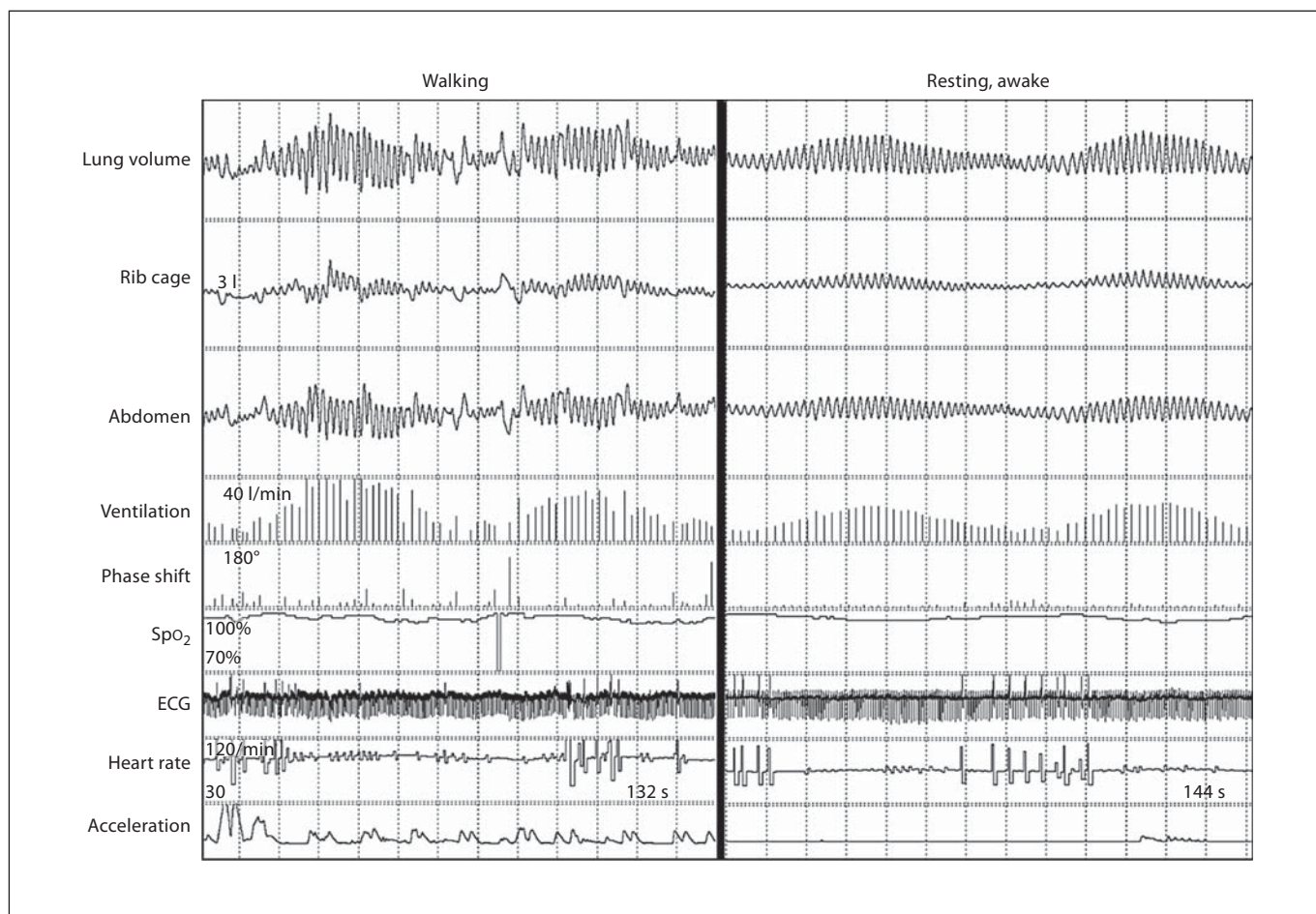


Fig. 1. Breathing pattern recorded with a portable device incorporating respiratory inductive plethysmography, pulse oximetry, ECG and an accelerometer in an ambulatory patient with severe heart failure. The left panel shows a period of walking, the right panel a period of quiet rest during daytime. Waxing and waning of the rib cage and abdominal excursions and of minute ventilation derived from the calibrated inductance sensors reveal periodic breathing with subtle oscillations in oxygen saturation (SpO_2). Modified from Brack et al. [5].

harms the failing heart. Quality of life (QoL) and sleep as well as ventricular function suffer from frequent periodic breathing, and CSR has been identified to shorten the life of heart failure patients. Pharmacological and non-pharmacological therapies are able to suppress or counteract CSR, and treatment has been shown to improve ventricular function as well as QoL [1, 5]. Noninvasive ventilation, including continuous positive airway pressure (CPAP) support, currently appears to most powerfully counteract CSR, but the jury is still out on whether noninvasive ventilation may also prolong the lives of heart failure patients. We reviewed the current literature on prevalence, risk factors, consequences and therapies of CSR in patients with CHF.

Prevalence and Importance of CHF and CSR

About 0.5% of the general population and 16% of people older than 75 years suffer from heart failure, respectively. Severe heart failure causes about 20% of all hospital stays in the elderly and carries a mortality of about 45% per year, which is higher than for most cancers [9, 10]. Sleep apnea often accompanies and aggravates heart failure. The reported prevalence of sleep-disordered breathing – either CSA or obstructive sleep apnea (OSA) – varies largely due to differences in patient selection and methodological issues. Most studies recruited outpatients from heart failure clinics, but some included hospitalized patients and the severity of heart failure, as

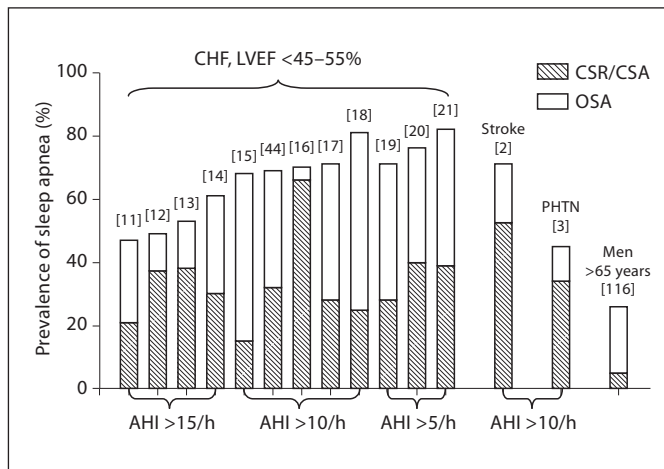


Fig. 2. Prevalence of sleep apnea in patients with CHF, stroke or pulmonary hypertension (PHTN) and in a community sample of men older than 65 years. The data were retrieved from published studies. Hatched and open columns represent the relative proportion of CSR/OSA and of OSA, respectively. The cutoff levels of the AHI used for definition of sleep apnea are indicated. Severe CHF was defined by an LVEF <35–45%. In this group of patients, the prevalence of sleep apnea is very high (47–82%) due to a high prevalence of both CSR and OSA.

sessed either by echocardiography or clinically, varied widely. The apnea-hypopnea index (AHI) that defined sleep apnea ranged from 15 to 5 cycles per hour and, accordingly, the prevalence varied from 47 to 82% and from 21 to 66% for sleep-disordered breathing and CSR in patients with CHF, respectively [2, 3, 11–21] (fig. 2). Thus, CSR is not limited to severe heart failure but may also occur at moderate stages of CHF with a left-ventricular ejection fraction (LVEF) between 35 and 45% with milder functional impairment (NYHA II). Although many studies reported a predominance of CSR in CHF patients, OSA was quite common as well [22] (fig. 2).

In addition to left-ventricular failure, CSR is also associated with right-heart failure secondary to pulmonary hypertension [3, 23] and with cerebrovascular stroke [2, 24, 25]. The highest prevalence of CSR occurred in hospitalized patients with severe CHF and/or stroke [2, 5, 26, 27] (fig. 2).

Risk Factors for CSR

Oldenburg et al. [20] recently screened 700 patients with CHF referred to a cardiology division for sleep apnea. Among those with an LVEF <40%, 40% had CSR/

CSA. As compared with those without sleep-disordered breathing, patients with CSR/OSA were slightly older, predominantly male and had more severe CHF as reflected in a higher NYHA functional class and a lower LVEF. Elevated pulmonary capillary wedge pressure is associated with hypocapnia, and both have been identified as risk factors for CSR [28, 29]. In addition, patients with CSR had a higher prevalence of atrial fibrillation and a reduced exercise capacity [20]. Mared et al. [16] found age to be the most important risk factor for CSR.

Consequences of CSR

Patients with CHF are less physically active if CSR occurs [30]. In 22 patients with mild to moderate CHF, actimetry was recorded to monitor the circadian activity pattern over the course of 2 weeks. Half the patients had predominantly CSA. On average, patients with CHF and CSA spent more time resting at night and were less active during the day. In addition, their sleep was frequently interrupted by movements, presumably due to arousals associated with apnea [31].

CSR also impairs the QoL of patients with CHF. Carmona-Bernal et al. [32] evaluated patients with and without CSR with two QoL questionnaires. The Minnesota Living with Heart Failure questionnaire focuses on domains such as physical activity, fatigue, social relations and mood, which are typically affected by CHF. The Functional Outcome of Sleep Questionnaire evaluates domains affected by sleep disorders such as productivity, activity and vigilance. Both questionnaires revealed impaired QoL in patients with CSR, highlighting the clinical relevance of CSR [32].

We have recently evaluated the QoL of patients with CSR associated with idiopathic pulmonary hypertension. Sleep studies in 38 consecutive patients identified 4 patients with predominant OSA and 15 patients with CSR (AHI >10 cycles per hour). Patients with CSR had impaired QoL mainly in the physical domain as assessed with the Minnesota questionnaire as well as with the generic SF-36 questionnaire. Remarkably, patients did not perceive subjective daytime sleepiness or other symptoms that would have clearly suggested sleep apnea [3].

Other studies have also confirmed that subjective sleepiness is not a prominent symptom in patients with CSR. Pepperell et al. [33] randomly treated 30 patients with CSR due to CHF either with therapeutic adaptive servoventilation (ASV) or with a sham treatment during

Table 1. Prognostic significance of CSR in patients with heart failure

	Lanfranchi et al. [43] 1999	Sin et al. [44] 2000	Corra et al. [45] 2006	Javaheri et al. [46] 2007	Brack et al. [5] 2007	Roebuck et al. [19] 2004	Luo et al. [21] 2010
Patients, n	62	66	133	88	60	78	128
Outcome	death, Tx	death, Tx	death, Tx	death	death, Tx	death	death
Risk associated with CSR ¹	+	+ 2.53	+ 5.7	+ 2.1	(+) 3.8	–	–
AHI defining presence of CSR cycles per hour	≥30	≥15	>30	≥5	≥15	>5	≥5
LVEF, %	23	22	23	24	26	20	36
Mean observation period, years	2.3	2.2	3.2	4.3	2.3	4.3	2.9
Remarks	patients with AF excluded	CSR treated	CSR during exer- cise and sleep	CSR treated	CSR during daytime	CSR treated	

¹ Hazard ratio controlled for several confounders, with + and – denoting increased mortality and equal mortality of CSR vs. no CSR, respectively. Tx = Survival without cardiac transplantation; AF = atrial fibrillation.

1 month. The baseline Epworth sleepiness score was nearly normal in both groups and did not change with treatment. In contrast, ASV revealed an improvement in sleep resistance time although several patients had a normal sleep resistance time from the beginning. In conclusion, patients with CSR often do not seem to perceive excessive sleepiness.

Additionally, CSR increases sympathetic nervous activity that harms the failing heart. Solin et al. [34] measured urinary catecholamines as markers of sympathetic nervous activity in patients with CHF (LVEF <35%), OSA and healthy controls. CHF patients excreted more norepinephrine than patients with OSA or healthy subjects; CHF patients with CSR excreted the largest quantities of norepinephrine. Multiple regression identified the severity of CHF as reflected by pulmonary capillary wedge pressure and nocturnal hypoxemia as strong predictors of urinary catecholamine levels. Elevated sympathetic nervous activity may immediately impair ventricular function so that brain natriuretic peptide, a marker of CHF, has also been found to increase during the night in patients with CHF and CSR [35, 36].

Sympathetic activity is increased during the hyperpneic phase of CSR and the heart seems to be most vulnerable to arrhythmia during hyperpnea [37]. 24-hour ECG monitoring revealed that patients with severe CSR had a significantly increased prevalence of nonsustained ventricular tachycardia and other arrhythmias as compared with patients with mild or no CSR [38]. In addition, patients with severe CSR had reduced heart rate variability, which suggests autonomic dysfunction [39]. A reduced percentage of beats with more than 50

ms variation in the RR interval was associated with mortality in patients with heart failure in an earlier study [40].

Prognosis of Patients with CSR and CHF

Hanly et al. [41] reported a mortality of 86 and 56% in patients with heart failure and CSR compared with patients without CSR during a follow-up of 2 years, respectively. In a recent retrospective cohort study, Javaheri et al. [42] found that both OSA and CSA in heart failure patients were largely underdiagnosed. Patients who were diagnosed and treated had a better 2-year survival than patients who were not tested (hazard ratio 0.33). The association of CSR with a two- to threefold increase in mortality sparked the hope that treatment of CSR would decrease mortality albeit other reports questioned an independent association of CSR and mortality in heart failure [19].

Autonomic dysfunction and cardiac electrical instability are potential explanations for the increased mortality in CHF patients with CSR. Lanfranchi et al. [43] observed 62 patients with severe CHF for a median of 28 months. Multiple regression revealed left atrial area measured by echocardiography and the number of CSR cycles per hour at night to be the most important independent predictors of transplantation-free survival. For example, the estimated mortality of a patient with a left atrial area of 55 cm² and 40 cycles per hour of CSR was more than 4 times higher than the mortality of a patient with a similar left atrial area but no CSR. Table 1 summarizes the most

recent studies on the impact of CSR on survival in patients with heart failure who were treated with all current standard cardiac medications [5, 19, 21, 43–46]. The outcome was either death or cardiac transplantation. The majority of studies found an increased mortality with a hazard ratio of 2.1–5.7 for CSR with only two exceptions [19, 21]. Patients and methods varied between studies, which may explain the different outcomes. For example, the AHI cutoff that discriminated patients with and without CSR varied between 5 and 30 cycles per hour. The patients' mean LVEF was very low with one exception and the observation time ranged from 2.2 to >4 years. Some studies excluded obese patients or those with atrial fibrillation, and CSR was treated with oxygen or CPAP in three studies; two studies included daytime CSR.

Corra et al. [45] studied patients with an EF <40%, who underwent sleep studies as well as spiroergometry; patients were followed for a mean of 3 years. When controlled for clinical and echocardiographic severity of CHF, cumulative survival without cardiac events was most reduced in patients who had both CSR during the night and during exercise testing.

CSR not only occurs during the night but also during the day. We recently found patients with severe heart failure who breathed periodically during about 10% of the day [5]. Continuous recordings of the breathing pattern in 60 patients with severe heart failure during their usual activities over 24 h at home revealed that CSR peaked at 1 p.m., 5 p.m. and 3 a.m. (fig. 3). Daytime CSR was associated with a higher mortality while nighttime CSR was not an independent predictor of survival during the observation time of more than 2 years. Patients with daytime CSR had a nearly 4-fold increased mortality even when controlled for age, gender and severity of heart failure.

Although data from the majority of studies suggest an independent effect of CSR on mortality in CHF, the association is not always strong. One reason for the variable association may be the varying prevalence of CSR within the same patient. Of 19 patients monitored over the course of 4 successive nights, 8 displayed a change in the severity of apnea from mild to severe if a cutoff of 30 cycles per hour was selected and 8 changed their predominant type of apnea from CSR to OSA and vice versa [47]. Moreover, some patients change their apnea type within the same night: while OSA may prevail in the first part of the night, CSR often dominates in the second part [48].

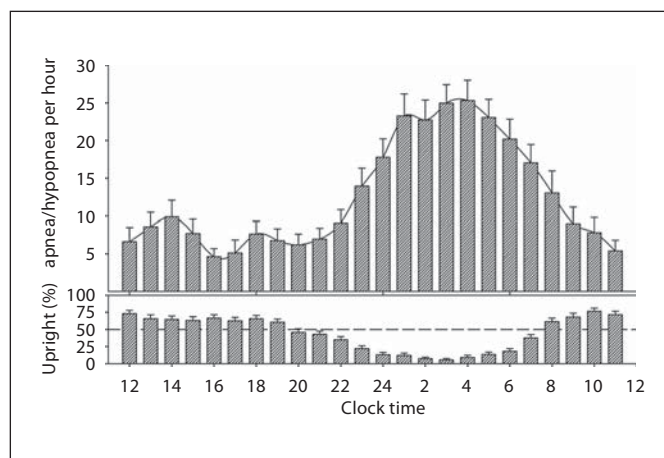


Fig. 3. Using portable monitoring devices in 60 ambulatory patients with severe CHF, the circadian prevalence of CSR was investigated. The highest number of CSR breathing cycles occurred during the night but CSR was also observed during daytime when patients were standing upright, performing their usual daily activities. Patients with a high prevalence of daytime CSR ($\geq 10\%$ of the day) had a much shorter survival without heart transplantation compared with patients with <10% of the day with CSR (hazard ratio 3.8). Modified from Brack et al. [5].

Pathophysiology of CSR

Left-heart failure that causes increased pulmonary venous pressure is regarded as a source of CSR. Elevated pulmonary venous pressure leads to pulmonary congestion that stimulates the pulmonary stretch receptors, which heighten the sensitivity of peripheral chemoreceptors to CO_2 through their vagal afferents [28, 49, 50]. Since CO_2 sensitivity increases, patients begin to hyperventilate and arterial CO_2 (PaCO_2) falls below the apnea threshold [51]. Moreover, hypoxia that follows apnea/hypopnea enhances postapneic hyperventilation. If chemical control prevails over cortical influence on the respiratory controller, as typically occurs during sleep, patients become apneic until PaCO_2 rises again above the apnea threshold. Thus, the alternating pattern of apnea and hyperpnea continues due to oscillations of the PaCO_2 around the apnea threshold [52, 53]. This periodic respiratory over- and undershoot causes additional sympathetic stimulation in patients who are already sympathetically stimulated through their heart failure [54].

Recent work confirmed the key role of CO_2 in the pathophysiology of CSR, which seems to be primarily determined by the difference in PaCO_2 during steady-

state ventilation (i.e. eupneic PaCO_2) and the respective apnea threshold for CO_2 [55, 56]. Patients with high ventilatory equivalents for CO_2 during exercise testing were particularly prone to CSR because the heightened ventilatory equivalent was an indicator of increased chemosensitivity to CO_2 [57]. The augmented chemosensitivity is probably caused by pulmonary congestion because pulmonary capillary occlusion pressure is inversely correlated with PaCO_2 during wakefulness [28, 49]. Since CSR persists up to 12 months after heart transplantation, albeit in a milder form, in about 20% of patients, periodic breathing appears to result not only from pulmonary congestion but part of the pattern seems to be learned and engraved in the respiratory controller [58, 59]. It has also become obvious that OSA and CSA are not strictly different entities but may share a common origin because OSA may dominate during the first half of the night, transforming to mainly CSA towards the morning in the same patient [47, 48]; in addition, the first breath of hyperpnea often has an obstructive component during CSR [60].

Treatment of CSR

Treatment of the Underlying Heart Disease

CSR fuels the vicious cycle of heart failure through recurrent sympathetic overstimulation and intermittent hypoxia so that the transformation of periodic into regular breathing has been a longstanding aim of cardiac therapy [61]. Pharmacological and interventional therapies primarily aim to ease pulmonary congestion through a decrease in preload and afterload, e.g. with diuretics and ACE inhibitors, to lessen sympathetic overstimulation through the blockade of β_1 -receptors, or to optimize cardiac output by electrical stimulation. Walsh et al. [62] found the ACE inhibitor captopril to improve sleep apnea and sleep quality in heart failure patients. Carvedilol, a β -blocker commonly used for the treatment of CHF, has been demonstrated to reduce CSR in patients with CHF [63]. Atrial overdrive pacing was reported to reduce CSR in patients with heart failure, but these results could not be reproduced by several consecutive studies [64–67]. Cardiac resynchronization with biventricular pacemakers has repeatedly been reported to more than halve CSR in patients with severe heart failure and ventricular asynchrony. Kara et al. [68] found a significant improvement of CSA under active stimulation with atrial synchronized biventricular pacemakers in 12 patients with heart failure and an LVEF of $28 \pm 2.8\%$.

Cardiac resynchronization therapy has also been shown to improve sleep quality, QoL as well as cardiac pump function and patients' outcome. Therefore, this albeit very expensive therapy should be evaluated in patients with severe heart failure associated with ventricular asynchrony due to conduction abnormalities [69]. If cardiac therapy fails to reverse CSR, directly influencing the respiratory controller to smooth periodic breathing arises as the goal of therapy [9, 10, 70].

Pharmacotherapy of CSR

Theophylline increases respiratory drive and improves myocardial contractility so that periodic breathing decreases, but at the same time the drug doubles the serum concentration of renin, causes arrhythmias and possibly increases the risk of sudden death [71]. In a randomized study including 15 patients, treatment with theophylline for 5 days improved CSR but not cardiac pump function [72]. Andreas et al. [73] demonstrated that theophylline did not increase sympathetic nerve activity in heart failure patients in contrast to healthy controls, but plasma renin level doubled in both groups. Theophylline is therefore currently not recommended as a treatment of CSR.

Acetazolamide is a carboanhydrase inhibitor that causes renal loss of bicarbonate. The resulting metabolic acidosis stimulates respiration and reduces periodic breathing by increasing the difference between the eupneic PaCO_2 and the respective apnea threshold. In a short randomized trial of 12 patients with heart failure, acetazolamide decreased periodic breathing by 38% and improved daytime sleepiness [56], but since long-term results are lacking, the drug may only be tried in selected patients under careful supervision.

Respiratory disturbances might be aggravated by arousals, which destabilize ventilation. In order to suppress arousals, Younes et al. [74] administered pentobarbital in a placebo-controlled animal trial. However, the authors found serious blood gas alterations with prolonged hypoxia. Data on the suppression of arousals in humans are not yet available.

Oxygen and Carbon Dioxide Inhalation

Supplemental oxygen increases the oxygen supply to the left ventricle and additionally may reduce reflex activation of the peripheral chemoreceptors. Oxygen suppresses periodic breathing because it blunts the hypoxic respiratory drive and the consecutive hyperventilation. However, data from clinical studies show conflicting results. Thus, nocturnal oxygen administered over 1–4

weeks cut CSR by half, decreased nocturnal norepinephrine excretion and increased maximal oxygen uptake during exercise because of improved physical performance [75–78]. Conversely, Gold et al. [79] found that supplemental oxygen may increase the frequency of OSA in patients with mixed sleep apnea. Moreover, LVEF and the patients' QoL did not improve [75, 77, 78, 80]. In contrast, recent studies also found that nocturnal oxygen improves QoL and cardiac function in heart failure patients [81, 82]. The Canadian Positive Airway Pressure Trial for Heart Failure Patients with Central Sleep Apnea (CANPAP) post hoc analysis showed that optimal suppression of respiratory disturbances is crucial to lessen mortality in heart failure patients with sleep-related breathing disturbances [83]. Since bilevel pressure support ventilation or ASV has been found to suppress CSR better than oxygen [84], oxygen may be reserved for patients who cannot tolerate noninvasive ventilation.

Inhalation of supplemental CO₂ or addition of artificial dead space suppresses CSR through a permanent elevation of PaCO₂ above the apnea threshold [85–88]. In a recent trial including 6 patients without heart failure, Thomas et al. [89] found that the addition of computer-controlled CO₂ at an inspiratory concentration of 0.5–1% through a CPAP circuit was very effective in the treatment of CSR. Since increased PaCO₂ can cause sympathetic stimulation and because trials of long-term effects of CO₂ augmentation are lacking, this therapy remains experimental [90]. The disadvantage of permanently elevated PaCO₂ could perhaps be overcome by dynamic application of a low inspiratory concentration of CO₂ as recently shown by Mebrate et al. [91] in a sophisticated computer model.

Positive Airway Pressure Ventilation

Over the past 10 years, the application of CPAP has repeatedly been shown to reduce CSR, to improve left-ventricular function and to decrease nocturnal norepinephrine excretion in patients with heart failure [92–94]. CPAP increases intrathoracic pressure, which decreases both afterload by lowering transmural cardiac pressure and preload by lowering the venous return, so that cardiac function improves in patients with high ventricular filling pressures [95–97]. Additionally, CPAP may interrupt CSR by counteracting the periodic oscillations of the end-expiratory lung volume during CSR [98]. In a randomized trial with 66 patients over 5 years, CPAP improved LVEF by 7% and decreased the combined rate of mortality and transplantation in the group of 29 pa-

tients with CSR while the 37 patients without CSR did not benefit from CPAP [44]. Based on these results, a large randomized multicenter trial including 258 patients with heart failure and CSR was performed in Canada (CANPAP) [99]. 128 patients were treated with CPAP and were compared with 130 matched patients without CPAP therapy. CPAP reduced CSR, improved nocturnal oxygen saturation, enhanced LVEF by 2%, reduced nocturnal norepinephrine excretion and also prolonged 6 min walking distance. Despite all these advantages of CPAP therapy, the treated patients had a lower transplantation-free survival compared with untreated patients during the initial 18 months of the trial; after 18 months, the survival rate was similar in both groups. The trial was terminated early because of the higher mortality in treated patients while mortality in untreated patients and patient recruitment were unexpectedly low. The converse effect of CPAP on mortality compared with the promising pilot study was explained by improved pharmacological treatment of heart failure in the past years. The addition of β -blockers that has become a mainstay of heart failure therapy in the period in between the pilot study [44] and the CANPAP trial [99] may have weakened the harmful influence of CSR and its consecutive sympathetic overstimulation on the failing heart. Other reasons for the divergent results of the CANPAP trial compared with the preceding study may be the lower compliance of patients with CPAP (4.3 vs. 5.6 h/day), the lower CPAP pressure (8 vs. 10 cm H₂O) and the lack of statistical power of the CANPAP trial because of the unforeseen low mortality in the control group [70]. In a post hoc analysis, only the subgroup of patients in whom CPAP suppressed CSR successfully (AHI <15 cycles per hour) benefited with increased left-ventricular function and transplantation-free survival compared with patients who responded insufficiently (AHI >15 cycles per hour) so that only good responders may profit from CPAP [83]. As a result of the CANPAP trial, CPAP can no longer be regarded as the standard therapy of CSR, but CPAP may still be beneficial in a subgroup of patients with high (>12 cm H₂O) left-ventricular filling pressure and without atrial fibrillation [100, 101]. As CPAP has been shown to improve survival in responders, a CPAP trial seems to be a reasonable first step of ventilatory support for heart failure patients with CSR. However, this trial should be closely monitored and ASV should be used if CPAP fails.

The disputed benefit of CPAP in the treatment of CSR and the patients' problems with CPAP compliance has spawned interest in alternative modes of noninvasive

ventilation. While CPAP maintains the same pressure level during expiration and inspiration, pressure support ventilation operates at a lower pressure during expiration and a higher pressure that actively supports inspiration. In contrast to CPAP, pressure support ventilation has the option to ventilate the patient during apnea and to support respiration during hypopnea. Pressure support ventilation can be administered in different algorithms for the treatment of CSR: bilevel positive airway pressure (BPAP) in spontaneous (S) or timed (T) or spontaneous/timed (ST) mode and ASV.

BPAP modes apply constant pressure support during inspiration. BPAP S only supports the patient's spontaneous ventilation while BPAP T or ST generates mandatory breaths in case of breathing pauses. Therefore, BPAP ST or T actively ventilates the patient if his/her own ventilation is insufficient. ASV (also named auto servoventilation or anticyclic modulated ventilation) supports inspiration minimally during hyperpnea and maximally during apnea/hypopnea so that, based on sophisticated algorithms, pressure support acts anticyclically to the cycles of CSR. Expiratory pressure is manually or automatically titrated in order to eliminate obstructive breathing disturbances. Similar to BPAP ST/T, ASV devices also generate mandatory breaths in case of apnea [102].

In a couple of small studies, BPAP ventilation in ST mode was somewhat superior to CPAP in suppressing CSR [51, 103]. Köhnlein et al. [51] compared the efficacy of BPAP ST with CPAP in a cross-over study for 2 weeks each with a 2-week washout period in between in patients with CSA and chronic CHF. Both modes improved respiratory disturbances, subjective and objective parameters of sleep quality and also left-ventricular function with no significant difference between them [51]. Dohi et al. [104] administered BPAP ST to a small group of patients who did not sufficiently respond to CPAP. They reported a further reduction in respiratory disturbances in 9 subjects. In contrast, Johnson et al. [105] found that bilevel in ST or T mode was more likely to worsen than improve central breathing disturbances, including CSR. As the body of evidence on bilevel therapy is very limited and the results are conflicting, BPAP cannot be generally recommended for treatment of CSR.

Compared with CPAP and BPAP, ASV more powerfully suppressed CSR; at the same time, sleep quality, QoL, left-ventricular function and exercise capacity improved with ASV, and norepinephrine excretion was suppressed [33, 84, 106–109]. Teschler et al. [84] compared oxygen, CPAP, BPAP ST and ASV for one night each in a group of 14 patients. Although BPAP ST showed

a better improvement of the mean CSA index as compared with oxygen and CPAP, individual results varied widely. In contrast, ASV normalized the CSA index in almost all patients. Peperell et al. [33] administered effective or subtherapeutic ASV for 1 month to 30 patients with chronic heart failure and mainly CSR/CSA. Effective ASV was superior in improving respiratory disturbances, daytime performance, cardiovascular and sympathetic markers. Philippe et al. [106] proved that ASV was superior to CPAP in terms of respiratory disturbances, heart function, QoL and compliance over 6 months. In addition, Morgenthaler et al. [107] showed that ASV was superior to BPAP ST in a heterogeneous population of patients with CSA/CSR, complex sleep apnea and mixed sleep apnea. ASV was also able to suppress CSR below 15 cycles per hour in heart failure patients who remained refractory under CPAP and BPAP ventilation [110].

In clinical practice, many patients suffer from coexisting OSA and CSR/CSA rather than pure CSR/CSA. In two prospective observational studies two different algorithms of ASV proved to effectively suppress all types of respiratory disturbances and to improve sleep quality as measured by sleep stages and arousals with no difference between patients with and without cardiovascular diseases [111, 112]. Kasai et al. [113] confirmed these results in a CPAP controlled trial over 3 months in 31 heart failure patients. Since patients with CSR infrequently suffer from daytime sleepiness, compliance with positive-pressure therapies is often low and therefore the finding that compliance with ASV was 2 h per day higher than with CPAP is very important [106]. However, it seems very important to focus on problems with mask and interface. Pusalavidyasagar et al. [114] described a higher prevalence of interface problems in patients with complex sleep apnea. Active or passive closure of the upper airways can be supposed if an increase in pressure support is unable to overcome breathing disturbances [60]. These phenomena should be primarily considered in case of treatment failure with ASV [102, 112].

Although preliminary data from a CPAP controlled trial over 12 months in patients with heart failure showed significantly greater improvement of central breathing disturbances with ASV [115], large studies on survival and cardiovascular outcomes are lacking. Nevertheless, ASV currently appears to be the most promising mode of ventilation in the treatment of CSR.

Conclusion

CSR is highly prevalent and harmful in patients with CHF. Since the treatment of CSR has been shown to improve cardiac function and QoL, sleep studies should be performed and treatment of CSR should be tried in patients with severe heart failure. Albeit the proof that treatment of CSR lowers mortality remains to be confirmed,

CSR should be treated to fight the debilitating symptoms of severe heart failure. Currently, ASV seems to be the most efficient treatment for CSR. Large randomized controlled trials of the long-term effects of ASV on morbidity and mortality in patients with severe heart failure and CSR are under way and their results are expected in the next few years.

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